Wyeth

February 2, 2004

Dockets Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0497, FDA draft guidance for Industry on Pharmacogenomic Data Submissions, November 2003 (68 FR, 62461-62463)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the FDA's draft guidance dated November 2003 on *Pharmacogenomic Data Submissions.*

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biologics and over the counter medications. As such, Wyeth is committed to the development of innovative drugs using new and emerging technology, such as genomics in drug development.

Wyeth commends and endorses the FDA initiative to provide early guidance on submission of pharmacogenomic (PG) data that will facilitate the scientific progress of this emerging technology referred to as pharmacogenomics. As a member of both the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Association (BIO), Wyeth has contributed to and supports the comments submitted by both of these organizations.

In addition, we are submitting the following comments and suggestions for your further review and consideration in the preparation of the final guidance on Pharmacogenomic Data Submissions.

I. General Comment

This guidance answered several issues raised by the Industry to the FDA proposal of providing a process for sponsors to submit exploratory pharmacogenomic data to the FDA. Implementation of this proposal should allow scientific discussion and learning to proceed without the fear that the

FDA will make regulatory decisions or unnecessary requests based on exploratory data.

The scope of the guidance is adequate to provide general guidance to companies who want to submit pharmacogenomic data voluntarily. Of significant note is the use of algorithms as decision trees to determine when and how to submit PG data. The decision point within the algorithms would be more applicable if they were based on how the data would be used. For example, under an IND, data required by the Code of Federal Regulations is generally used to support the safety of clinical investigations and/or provide scientific rationale. Exploratory data is used for research purposes only and is not required to be reported to an IND. Any exploratory data not used to support the safety and efficacy of clinical trials or to substantiate a scientific position would qualify for voluntary submission of a full report. Under an NDA, the exploratory data is required to be reported in a synopsis. This approach would eliminate the confusion of whether the data to be reported is from a well-established valid biomarker, probable valid marker or exploratory research. We also recommend that guidance be added on the extent of PG data from preclinical studies versus clinical studies that should be included in voluntary submissions for each algorithm. It is not clear if the agency would request voluntary submission of a full data set of global expression in animals and in man when only specific gene expression profiles for exploratory study are submitted.

Wyeth also recommends a clear and detailed description of the procedure that will be implemented to ensure that an individual FDA reviewer's interpretation of a voluntary genomic data submission (VGDS) would have appropriate oversight and be approved by senior FDA management. While this is addressed in lines 498 – 509, the process must ensure the use of such data by the FDA is as intended in the guidance document and not lead to unreasonable requests for additional data that may delay drug development. The procedures should also define mechanisms for sponsors to alert FDA senior management of unreasonable requests.

Specific comments by Wyeth are provided below as suggestions to further enhance the PG data submission guidance and encourage its use in the development of safer and more effective medicines.

II. Specific Comments

Comments that follow will address each section by line in the guidance.

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Introduction Section: (Line 16)

Line 30: The sentence "The FDA plans to provide guidance on these issues at a future time" should be moved to the end of line 33 and add the clause: *"however, data from other "omic" technologies is likely to be relevant to the principles and policies discussed in this specific guidance for pharmacogenomic data.*

Background Section: (Line 41)

Line 95. At the end of this sentence, state: " In addition, an FDA/Industry workshop on Genomic Data Submissions was held Nov 13-14, 2003 to discuss this guidance in an open forum for public comment".

Submission Policy: (Line 102)

A. General Principles Section:

This section provides the principles for interpreting the existing codified regulations for reporting pharmacogenomic data generated during the three stages of applications, which are investigational drugs, new drugs and marketed drugs. Wyeth recommends addition of the following additional sentences on line 120: *"When an application is submitted for IND, NDA or BLA review or is approved, pharmacogenomic studies are required to be reported either as a synopsis, abbreviated report or full report, depending on the use of the data. Voluntary data submission of exploratory data may be submitted as a full report to the IND at any time during the investigational phase or at the time of NDA application and NDA annual updates."*

Line 128 defines a pharmacogenetic test and should be supported with additional cross-reference to lines 591 to 611 for guidance to biomarker definitions. Examples of known biomarkers should also be referenced here; and distinctions between biomarkers of non-clinical, clinical pharmacology and clinical efficacy studies should be made in order to appropriately apply the VGDS to the stage of drug development. More clarity on analytical validation and

clinical validation parameters should be elements of the threshold definition recommendations for exploratory research data. For example, Line 139 should clarify the criteria for significant association required to establish a valid biomarker. We also suggest that "known" valid and "probable" valid biomarkers as defined in the guidance document be grouped as valid biomarker data to differentiate it from exploratory data.

B. Specific Uses of PG Data in Drug Development and labeling

This section introduces the proposed "specific uses" of PG data that would require submission or recommend voluntary PG data submission. Please refer to opening comments on the first page of this response document recommending application of the use of the data as the basis for required or voluntary submissions.

Voluntary Submissions of Exploratory Pharmacogenomic Research Data - -Line 221

Line 238 should highlight specific guidance that differentiates non-clinical (safety and pharmacology) studies, clinical pharmacology and clinical safety and efficacy stages of drug development in using the decision algorithms.

Line 240 should define the makeup, qualifications and authority of the Interdisciplinary Pharmacogenomic Review Group (IPRG) Please refer to the opening comments of this response in reference to the recommended policies and procedures for reviewing PG submissions.

Submission of Pharmacogenomic Data - Line 245.

As noted on the first page of this response, the decision point within the algorithms would be more applicable if they were based on how the data would be used. Please see our comments under the heading, "General Comments" starting on page 1.

If possible, provide guidance on the extent of PG data from preclinical studies versus clinical studies that should be included in voluntarily submissions for each algorithm. For example, we do not recommend the agency request voluntary submission of global

expression in animals and in man when only specific gene expression profiles for exploratory study are submitted voluntarily. Also, we suggest that the guidance document indicate that exploratory data be defined by the sponsor either prospectively in study protocols or retrospectively in study reports.

Format and Content of a VGDS - Line 408

Lines 419 thru 425 regarding the purpose of VGDS should be moved to and inserted at line 244.

Lines 436 and 441 reflect the wide recommendation for VGDS data format, from an article submitted to a peer-reviewed publication or a rather complete report on gene expression microarray experiments. Another approach to recommend would also encourage initial VGDS submissions in either a written synopsis or presentation format. When the FDA analysts and IPGRG have specific areas of analytical interest that require more complete data sets, they could request them from sponsors. For example, a request for .cel files would be appropriate if the agency would like to examine alternative algorithms for converting the data into expression levels. Data from all genes could be submitted to enable alternative approaches for normalizing the data or doing class prediction. Results of such testing should be shared with the sponsor and any suggested follow up actions agreed to by both senior FDA management and the sponsor.

Lines 441-467 indicate that all data on all genes should be included in the report. The FDA should assure that submitted VGDS data will not be used for other clinical associations with genes already known as valid biomarkers or genes that will become valid biomarkers in the future. While lines 458-460 cover the validation of gene expression data by "conventional technologies", we recommend that validation of expression profiles, gene by gene using RT-PCR or Northern assays, for example, should not be required or recommended. In many situations, the expression results may be a pattern of genes that is diagnostic or prognostic and not amenable to validating every gene in the signature.

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FDA Review of Pharmacogenomic data - (Line 487)

This section should be rewritten for clarity to address the following concerns.

Lines 489-496 – delete: "The FDA has received many questions about the use of pharmacogenomic data in the application review process....." since lines 56-57 highlight the concerns.

Lines 498 to 509: As noted above in the opening comments, Wyeth would like to strongly recommend a clear description of the process and procedure that will be implemented to ensure that an individual FDA reviewer's interpretation of VGDS would have FDA oversight and be approved by senior FDA management. While this is addressed in lines 498 – 509, the process must ensure the use of such data by the FDA is as intended in the guidance document and not lead to unreasonable requests of sponsors for additional data that may delay drug development. The procedures should also define mechanisms for sponsors to alert senior management of unreasonable requests. For example, the guidance should address the constituents of IPRG in terms of offices, divisions, and laboratories of the disciplines that will make up IPRG and the reporting structure of the IPRG. It would also be helpful to list the roles and responsibilities of the group, including interactions within the FDA as well as sponsors. It would also be helpful to present a decision tree algorithm for the IPRG for notification of the sponsor when a VGDS may be significant in relation to other information available to the IPRG. Mechanisms for exchange of scientific information should be suggested. The FDA should consider, for example, setting up a public committee to routinely meet and discuss how VGDS are generating new knowledge that is applicable to all stakeholders. Additionally, procedures need to be in place to maintain the confidentiality of the company and product under development.

Lines 511-515 - the paragraph should be more specific that toxicogenomics will not replace or override animal and in vitro toxicology data. Lines 511 to 515 should clearly indicate that there are currently no valid or probable valid biomarkers in animal PG studies that would replace the current methods of animal and in vitro toxicology, that such data will be viewed as exploratory

VGDS until proven and accepted by the scientific community and that such data from VGDS will have no regulatory impact on the drug under development or approved.

Lines 517 thru 540 should be rewritten to clearly illustrate case examples of pharmacogenomic data use in drug labeling, and to describe the circumstances under which it might be required to use PG testing to restrict drug use for safety and or efficacy reasons. An algorithm to explain the FDA requirements of co-approval of PG diagnostic tests would be helpful.

There has been a growing number of pharmacoepidemiologic studies conducted to investigate safety concerns of drugs raised from postmarking adverse event reports. Identifing risk factors or high-risk subpopulations has often been an important part of the objectives for this type of study. Genotype or gene expression profile could be studied as potential risk factors along with other variables such as age, gender, race, co-morbidity, and co-medications. Therefore, it would be useful to provide some guidance regarding how the PG data collected in pharmacoepidemiologic studies would be submitted or used by the FDA.

Additionally, how would the FDA review PG data collected from observational, non-interventional studies, when they are not associated with a drug, either investigational or approved?

Appendix D should be either referenced here or discussed to illustrate the above points.

Lines 551 to 571 should be sub-headed. The sub-heading could be: "FDA encourages targeted drug therapy."

Line 851: Correct the number "IV.B.2" to "IV.A.2"

Appendix E should be rewritten to incorporate the same wording of the decision boxes on the 3 charts in Appendices A, B and C. It should show that exploratory PG data would only be required for submission if the product is submitted as an NDA or BLA and only then as a synopsis. Full reports of PG data may be submitted voluntarily to the IND, NDA, BLA

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or approved product file when abbreviated or synospsis reports are required.

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance, and trusts that the Agency will take these comments into consideration when preparing the final guidance on Pharmacogenomic Data Submissions.

Sincerely,

Roy J. Baranello, Jr.
Assistant Vice President,
Worldwide Regulatory Affairs